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SARIN AND SOMAN: OBSERVATIONS ON
ACCIDENTAL EXPOSURES

Frederick R. Sidell

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Aberdeen Proving Ground, Maryland

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) The case histories of five patients accidentally exposed to anticholinesterase compounds (sarin or soman) are presented. The circulating cholinesterase of one patient severely exposed to soman was refractory to oxime reactivation; this patient also had psychological sequelae which were ameliorated by scopolamine. In three patients who had mild manifestations of sarin intoxication the initial rate of recovery of plasma cholinesterase paralleled the recovery of their ability for adaptation to the dark, or loss of miosis. An anticholinergic compound with high central nervous system affinity, such as scopolamine, should be tried further when psychological morbidity follows anticholinesterase compound intoxication.		

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DIGEST

The case histories of five patients accidentally exposed to anticholinesterase compounds (sarin or soman) are presented.

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FOREWORD

The work described in this report was authorized under Project/Task No. 1W662710AD2502, Medical Defense Against Chemical Agents, Prophylaxis and Therapy for Lethal Agents. This work was started in June 1965 and completed in February 1973.

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SARIN AND SOMAN: OBSERVATIONS ON ACCIDENTAL EXPOSURES

I. INTRODUCTION.

The organophosphate anticholinesterase (ChE) compounds are widely used in pharmacology, medicine, and agriculture. Accidental human poisoning by these compounds occurs among farmers, crop dusters, and among children; the former two use the compounds as insecticides. As many of these compounds are readily available they are used in suicide attempts.

This report describes the sequence of events following accidental exposure to the potent anticholinesterases sarin* (four people) and soman** (one person). To our knowledge these are the first reports of accidental exposure to these substances. Since a general review of the pathophysiology and principles of therapy of anticholinesterase compound poisoning has recently been published,¹ the discussion will be limited.

Among our observations were the following:

a. Psychiatric sequelae have been reported^{2,3} after anticholinesterase compound poisoning and are probably more common after severe intoxication than usually noted. Two patients had these complications.

b. Scopolamine hydrobromide, which in normal individuals causes a decrease in cognitive ability and mental functioning,⁴ paradoxically caused a temporary improvement in the mental status of one patient in the immediate recovery period.

c. Some pyridinium oximes (e.g., 2-pyridinium aldoxime methochloride; 2-PAMCl)[†] can reverse the cholinesterase inhibition caused by organophosphate anticholinesterases and are valuable adjuncts in therapy. The effectiveness of the oxime varies with the inhibitor and generally decreases as time after inhibition increases, as many organophosphates will become irreversibly bound to the enzyme rendering enzyme-inhibition complex nonamenable to oxime reactivation. Soman produces a bond that within minutes becomes refractory to oxime displacement.^{5,6} This refractoriness to oxime was noted in a patient poisoned with soman as his inhibited circulating cholinesterases appeared to be unaffected by 2-PAMCl. Despite this, his clinical recovery was consistent with the severity of his exposure.

II. CASE REPORTS.

A. Case 1.

This 33-year-old man had been working with small amounts of soman in solution when a syringe-needle connection broke, splashing some of the solution into and around his mouth. The concentration of soman was 25% (v/v) and the total volume was less than 1 ml. He immediately washed his face and rinsed his mouth with water, and was brought to the emergency room, (ER) about 9 a.m., 5-10 minutes after the accident. He was asymptomatic until he arrived at the ER when, as he later said, he felt "the world was caving in on me," and he collapsed. His past medical history was noncontributory. Physical examination showed him to be comatose and mildly cyanotic

*Isopropyl methylphosphonofluoridate

**Pinacolyl methylphosphonofluoridate, or (1, 2, 2-trimethylpropyl) methylphosphonofluoridate

[†]Indexed in C.A. subject indexes at Pyridinium, 2-formyl-1-methyl- chloride, aldoxime

with slightly labored respiration. Intravenous atropine sulfate (2 mg) was given and may have been partially responsible for his initial blood pressure of 180/80 and heart rate of 150. He had miosis (1-2 mm, bilaterally), markedly injected conjunctiva, marked oral and nasal secretions, moderate trismus and nuchal rigidity, prominent muscular fasciculations, and hyperactive deep tendon reflexes. Except for tachycardia his heart, lungs, and abdomen were normal.

Course.

Within a minute after he collapsed (about 10 minutes after exposure) he was given intravenous atropine sulfate and in the ensuing 15 minutes he received a total of 4 mg intravenously and 8 mg intramuscularly and pralidoxime chloride (2-PAMCl) was administered (2 gm over a 30-minute period in an intravenous drip). Supportive care in the first 30 minutes consisted of oxygen by nasal catheter and frequent nasopharyngeal suction. Bronchoconstriction and a decreased respiratory rate and amplitude were prominent; the former was more responsive to atropine therapy. He became cyanotic and attempts to insert an endotracheal tube were unsuccessful because of trismus. Since spontaneous respirations did not cease, a tracheostomy was not performed.

After the initial therapy his cyanosis cleared and his blood pressure and heart rate remained stable. He began to awaken in about 30 minutes and thereafter was awake and alert. Migratory involuntary muscular activity (fasciculations and tremor) continued through the day.

He improved throughout the day, but was generally uncomfortable and restless with abdominal pain and nausea throughout the day and night. Atropine (4 mg, iv) was required again at 11 p.m. (14 hours post exposure) after several episodes of vomiting. About 4 a.m. he was catheterized because of urinary retention.

His restlessness and intermittent nausea continued and about 5 a.m. (20 hours after exposure) he again vomited. Because the previous atropine had apparently caused urinary retention, this emesis was treated with a small dose (5 mg, im) of prochlorperazine, although phenothiazines have been reported to be deleterious in anticholinesterase compound poisoning^{7,8}. His general condition, including his discomfort, did not change. He vomited twice more between 7:30-8 a.m. (22-23 hours post exposure) and was again given atropine (4 mg, im). He voided small amounts several times, but catheterization was again necessary several hours later.

Several EKG's recorded on admission and during the first day showed sinus tachycardia. On the second day (25 hours after exposure and about 2 hours after atropine administration), his cardiac rhythm was irregular, and an EKG showed atrial fibrillation with a ventricular rate of 90-100 beats per minute. This persisted throughout the day and evening, but his cardiac rhythm was again regular sinus the next morning.

During the second evening (about 36 hours after exposure) he again became nauseated and had recurrent vomiting. Because of the occurrences of urinary retention and arrhythmia, presumably due to atropine, he was again given prochlorperazine (5 mg, im) at 10 p.m. and again at 2 a.m. Half an hour after the first dose he complained of transient "tingling" feelings over his body, but there were no objective changes. After the second dose he rested comfortably and slept soundly for 3-4 hours, his first restful sleep since the exposure. At 11 a.m. the next morning, he was restless and had an expressionless face, torticollis and athetoid movements. Diphenhydramine hydrochloride (50 mg, iv) promptly relieved these symptoms and signs, which are

characteristic of the extrapyramidal side effects of a phenothiazine. Throughout the remainder of his hospitalization the patient's physical condition improved, although he was treated with sulfisoxazole for 3 weeks for a urinary tract infection which developed after catheterization.

His psychiatric condition did not improve as rapidly as his physical condition. As the complications of the treatment for the physical effects subsided, evidence of lingering mental effects began to appear. A psychiatrist (J.S.K.), who saw the patient frequently, recorded that he seemed depressed, was withdrawn and subdued, admitted to antisocial thoughts, slept restlessly and fitfully, and had bad dreams. On the third day the patient was given scopolamine hydrobromide (5 μ g/kg, or 330 μ g, im) as a therapeutic trial. Psychiatric evaluation at the time of maximum scopolamine effect showed a slight but distinct improvement in mental status as he seemed more comfortable and performed better on several mental function tests (e.g., serial 7's) than before scopolamine. That evening he was given 1.8 mg of scopolamine (orally) at bedtime and slept much better for most of the night.

This nighttime benefit from scopolamine may have occurred because of its sedative properties, but the improvement in mental status during the day suggested a more specific action, as scopolamine in this dose produces a slight decrease in intellectual functioning in normal subjects.⁴ To investigate this further on 3 of the next 6 days the patient was given scopolamine (1.2 mg, p.o.)* and on the other 3 he received methscopolamine. Methscopolamine was chosen as placebo because it produces the same peripheral effects as scopolamine (mild xerostomia, tachycardia, etc.), but no central effects. The days of drug or placebo administration were randomly selected and the evaluating physician, a psychiatrist (J.S.K.), did not know which was given. Scopolamine was given on days 1, 3, and 6 and methscopolamine on days 2, 4, and 5. In addition to the clinical evaluation, the patient took an objective test of cognitive function, the Number Facility test,^{9**} every 2 hours each day.

On the basis of the patient's mood, the evaluator correctly identified the drug given each day. The patient was less depressed, more spontaneous, and appeared more alert on the days he received scopolamine. The NF scores are shown in figure 1. When he was given scopolamine, his scores tended to improve during the day; on the other days the trend was the opposite. Figure 1 also shows the highest daily score. Although the hourly or daily differences are not statistically significant, they do coincide with the clinical findings, suggesting a definite benefit from scopolamine.

There was no detectable RBC-ChE until about the 10th day after exposure (figure 1),¹⁰ †. Apparently neither the RBC nor plasma ChE was significantly reactivated by the initial oxime therapy, which reflects the rapid irreversible phosphorylation and hence refractoriness of the soman-inhibited enzyme to reactivation by oxime.

Hematocrit, hemoglobin, white blood cell count, prothrombin time, blood urea nitrogen, bilirubin, creatinine, calcium, phosphorus, serum glutamic oxaloacetic transaminase, alkaline phosphatase, sodium, potassium, chloride and carbon dioxide were all within normal limits the day of admission and on repeated measurements during his hospitalization.

* Unpublished observations of J. S. Ketchum indicate that an intramuscular dose is about 4 times more potent than an oral dose.

** This is a 3-minute addition task and the score is the number of problems solved correctly within this time.

† The ChE activity is expressed as a percentage of his last recorded value (at 4 months) (not shown) and it was assumed that at this time recovery was 100% complete. The method is one reported previously.

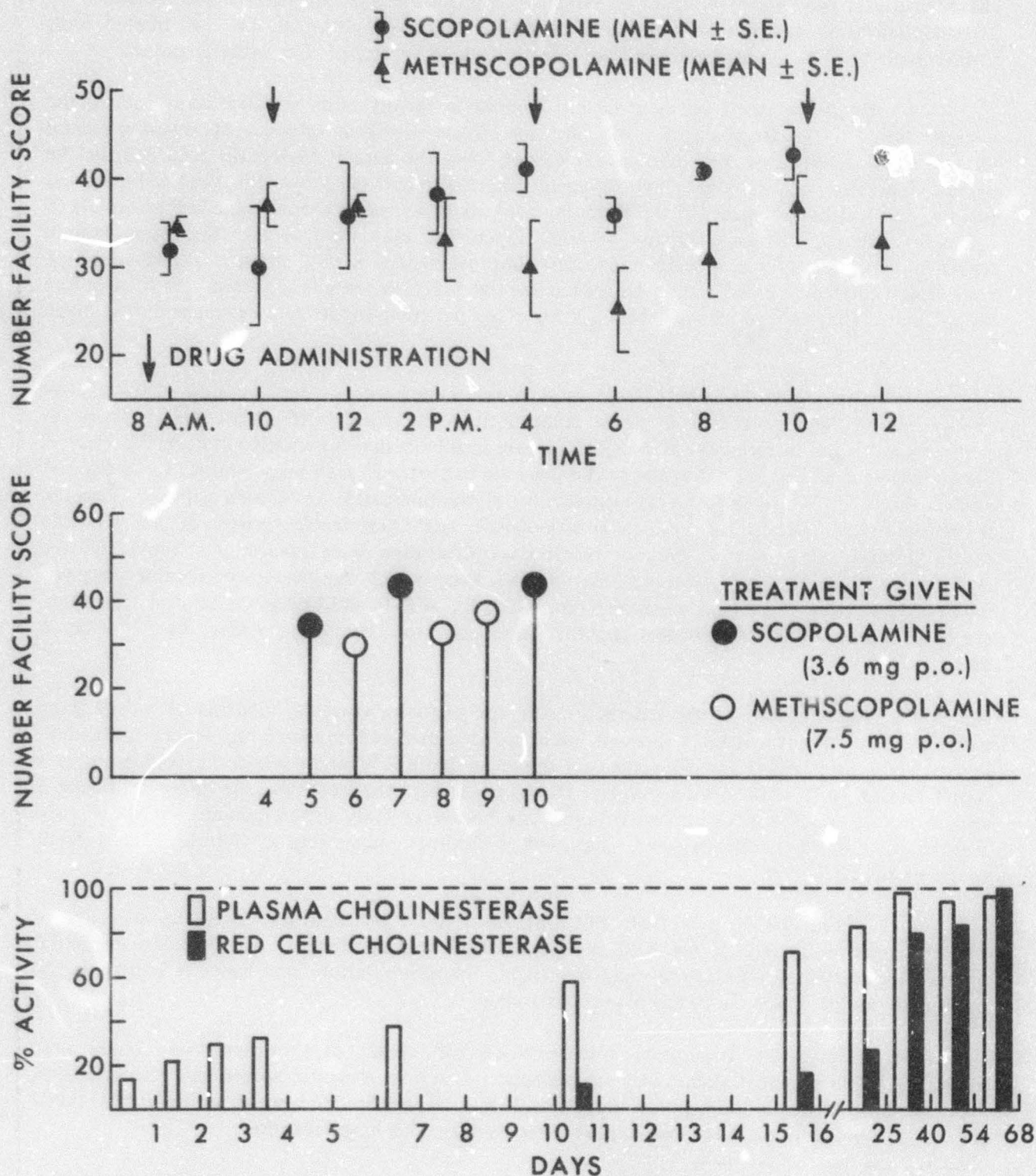


Figure 1. Upper: NF Scores of Patient 1 While He Was Receiving Scopolamine or Methscopolamine. Each point represents the mean of three days' scores.
 Middle: Highest NF Score Recorded on Each Day While Patient 2 Was Receiving Scopolamine or Methscopolamine.
 Lower: Time Course of RBC and Plasma ChE in Patient 2.

About five weeks after his initial admission, the subject again received scopolamine (5 mg/kg, im) and had a decrement in mental functioning, including a 25-30% reduction in NF scores, which are the findings in normal subjects. This contrasts with the paradoxical improvement in mental status seen earlier.

About a week later the psychiatrist noted that "he is probably close to his premorbid level intellectually and there is no evidence of any serious mood or thinking disorder."

A battery of standard psychological tests was given the subject 16 days, 4 months and 6 months after this accident. He scored well on the Wechsler-Bellevue IQ test with a slight increase in score on the arithmetic section at the later testings. He had high Hs (hypochondriasis) and Hy (hysteria) scales on the Minnesota Multiphasic Personality Inventory (MMPI) on the early test and their later improvement indicated to the examiner that he had a decreased concern about bodily function. He did poorly on a visual retention task (the object of which was to remember and then reproduce a simple drawing) on first testing as he attempted to improve already correct drawings, made several major errors, and showed poor motor control; his later tests were normal. On word association, proverbs, and the ink blot he was slow and sometimes used delaying tactics, had difficulty generating verbal associations, and failed the harder proverbs, responses, which in the examiner's opinion, were not consistent with his IQ. The results of his later tests were faster, imaginative, and indicated full use of his intellectual facilities.

When last seen, 6 months after his exposure, the patient was doing well.

B. Case 2.

This 52-year-old man had been cleaning a sarin-contaminated area and was wearing full protective gear, including a protective mask, which was later shown to have a crack in the voicemitter diaphragm, which should have been noticed when he donned and tested the mask. After complaining of an increase in oral and nasal secretions and difficult breathing, he left the area. Within minutes he was in marked respiratory distress and had copious secretions. He arrived at the emergency room 5-10 minutes after the first symptom.

On arrival, the patient was cyanotic and convulsing; his breathing was labored; muscular fasciculations, miosis, and marked salivation and rhinorrhea were evident. Because of the urgency of the situation, treatment was begun before he was examined more thoroughly.

Course.

Atropine sulfate, 2 mg iv and 2 mg im, was given immediately; then an intravenous infusion of pralidoxime chloride (2 grams in 150 ml of normal saline) was begun and oxygen was given through a face mask. An additional 2 mg of atropine (iv) was given several minutes later. In 2-3 minutes his respirations were less labored and the cyanosis had decreased. His blood pressure and heart rate were 190/110 mm Hg and 130 beats per minute, and regular. Marked muscular fasciculations were still present, but bronchoconstriction and secretions had diminished.

Twenty minutes after admission the first dose of pralidoxime chloride had been absorbed and another 2 gm was started. Because of the return of copious secretions more atropine (2 mg, iv) was given. About 30 minutes after admission he was awake, but intermittently irrational. Pertinent findings on examination were muscular fasciculations, bilateral wheezes, and S4 cardiac gallop, and marked miosis. He became nauseated and vomited a small amount.

For the next 20 minutes his respiration diminished in frequency and amplitude; 50 minutes after admission, he again vomited and then became more irrational, fought assistance (including the oxygen mask), and became cyanotic. More atropine (2 mg, im) was given and a third dose of pralidoxime chloride (2 gm) was begun. At 60 minutes after admission he again became comatose and totally apneic. Although rhonchi and wheezes were present throughout his pulmonary fields, adequate aeration was established by assisted respiration and his color improved. A nasogastric tube was passed because of gastric distention and repeated vomiting. An additional dose of atropine sulfate (3 mg) was given slowly, intravenously, because of increasing bronchoconstriction.

After 50 minutes of assisted ventilation feeble respiratory efforts returned, but air exchange was poor and intermittent respiratory assistance was continued for an hour more (until 3 hours after admission). At 2.25 hours after admission (1.25 hours after atropine) bronchoconstriction increased, but diminished rapidly when additional atropine sulfate (1 mg, iv) was given.

At about 2.5 hours after admission his sensorium slowly began to clear, he began to breathe spontaneously with adequate aeration, and his color remained good, although there were several more episodes of vomiting. At 9 hours after admission he felt well enough to walk around the ward although he was very weak and areflexic.

During a restless night he complained of numerous muscular pains and vomited twice more. The following morning (18 hours after admission) he had small but reactive pupils, clear lung fields, no cardiac gallop, and reactive deep tendon reflexes.

Red blood cell cholinesterase (RBC-ChE), in blood drawn after part of the first dose of pralidoxime chloride had been absorbed, was 0.35 micromoles/ml/min (or less than 7% of the subsequent value). RBC-ChE in a second sample drawn after pralidoxime administration was 5.59 micromoles/ml/min (within the normal range of 4.08-8.06 by the method used).¹⁰

An electrocardiogram (EKG) taken an hour after admission showed sinus tachycardia and marked depression of the ST segment in all leads. A second EKG, taken 18 hours after admission, showed elevation of the ST segment in leads I, aVL and V₁₋₃. At 24 hours after admission the ST segment recorded from the anterior chest leads was elevated and the T wave measured in leads V₄₋₆ was inverted. The following day, 42 hours after admission, the ST segment was elevated (leads I, aVL and V₂₋₆) and the T wave was inverted (leads I, II, aVL, and V₂₋₆). During this period the patient complained of generalized muscular pain and soreness, but even in retrospect did not describe a pattern typical of cardiac ischemia. The EKG pattern stabilized over the next few days. Then the ST segment became isoelectric, but the T wave inversions persisted for the next 4 weeks.

Because of these EKG changes he was hospitalized elsewhere. During the first 2 to 3 days he was very labile emotionally and had one episode of hysterical voice loss. He also complained of minimal, migratory chest pains and a slight productive cough. From the fourth day onward the patient was asymptomatic, and he had an uneventful recovery. After 2 weeks of bed rest his physical activity was gradually increased, and by the time of his discharge 2 weeks later (4 weeks post exposure), he was ambulatory and doing well. An EKG taken 4 months after exposure was entirely within normal limits.

At 4 months he was rehospitalized for complaints of easy fatigability, dyspnea on exertion, restlessness, and poorly localized pains in his chest abdomen. No physical causes were found for these complaints, but he was noted to have a marked depression associated with anxiety, crying spells, and restlessness. At 6 months, a psychiatrist felt that the patient had a depressive reaction with a great deal of anxiety about the intactness of his body arising from worry over his cardiac status. The evaluation was hindered by only meager knowledge of the patient's preexposure personality. He received psychiatric assistance throughout these months, but was lost to follow up when he retired and moved from the area. Approximately a year later (18 months after his exposure) word was received that he had died suddenly. The autopsy diagnosis was acute myocardial infarction, involving the posterior portions of both ventricles, the posterior part of the septum, and the anterolateral portion of the left ventricle; and marked sclerosis of the coronary arteries, with reduction of the lumen of the left coronary artery to about 30% and complete occlusion of the right coronary artery.

C. Cases 3, 4, and 5.

Three men, ages 27, 50, and 52 years, were brought to the emergency room because of sudden onset of rhinorrhea and slight respiratory discomfort. At the onset of symptoms they were working in a large room in which some containers of sarin were stored. Although there were other workers in the room, the three patients were together at one end where a leak was later found in one of the containers.

On examination all three patients had essentially the same signs and symptoms: very mild respiratory distress, marked miosis with slight eye pain, rhinorrhea, a moderate increase in salivation, and scattered wheezes and rhonchi throughout all lungs fields. No other abnormal findings were noted.

Course.

All three patients reported that their respiratory distress had decreased since its onset about 20 minutes before they arrived at the emergency room. The men were kept under observation for the next 6 hours, but no therapy was administered. They continued to improve and at the time of discharge from the ward they were asymptomatic except for a slight irritation in the eyes and decreased vision in dim light.

The patients were seen the next day and at frequent intervals thereafter for a period of 4 months. Each time they were seen their RBC and plasma ChE values were measured (figure 2) and photographs were taken of their eyes. The first photographs were taken the day of the exposure, but the patients were not adapted to the dark. On each visit thereafter a photograph was taken by electronic flash after the man had been in a completely dark room for 2 minutes. A series of photographs for one subject is shown in figure 3; the gradual increase in pupil size and decrease in conjunctival irritation are evident. The ratio of the diameter of the pupil to the diameter of the iris was calculated from a greatly enlarged photograph. This ratio (as a percent of the ratio obtained 3-4 months after exposure) and ChE levels are shown in figure 2. About 60-70% of the lost ability to adapt to the dark returned in 2 weeks, but complete recovery took 2 months.

III. DISCUSSION.

The general sequence of events with exposure to increasing amounts of vapor of an anticholinesterase compound are miosis, rhinorrhea, bronchoconstriction and excess salivary and

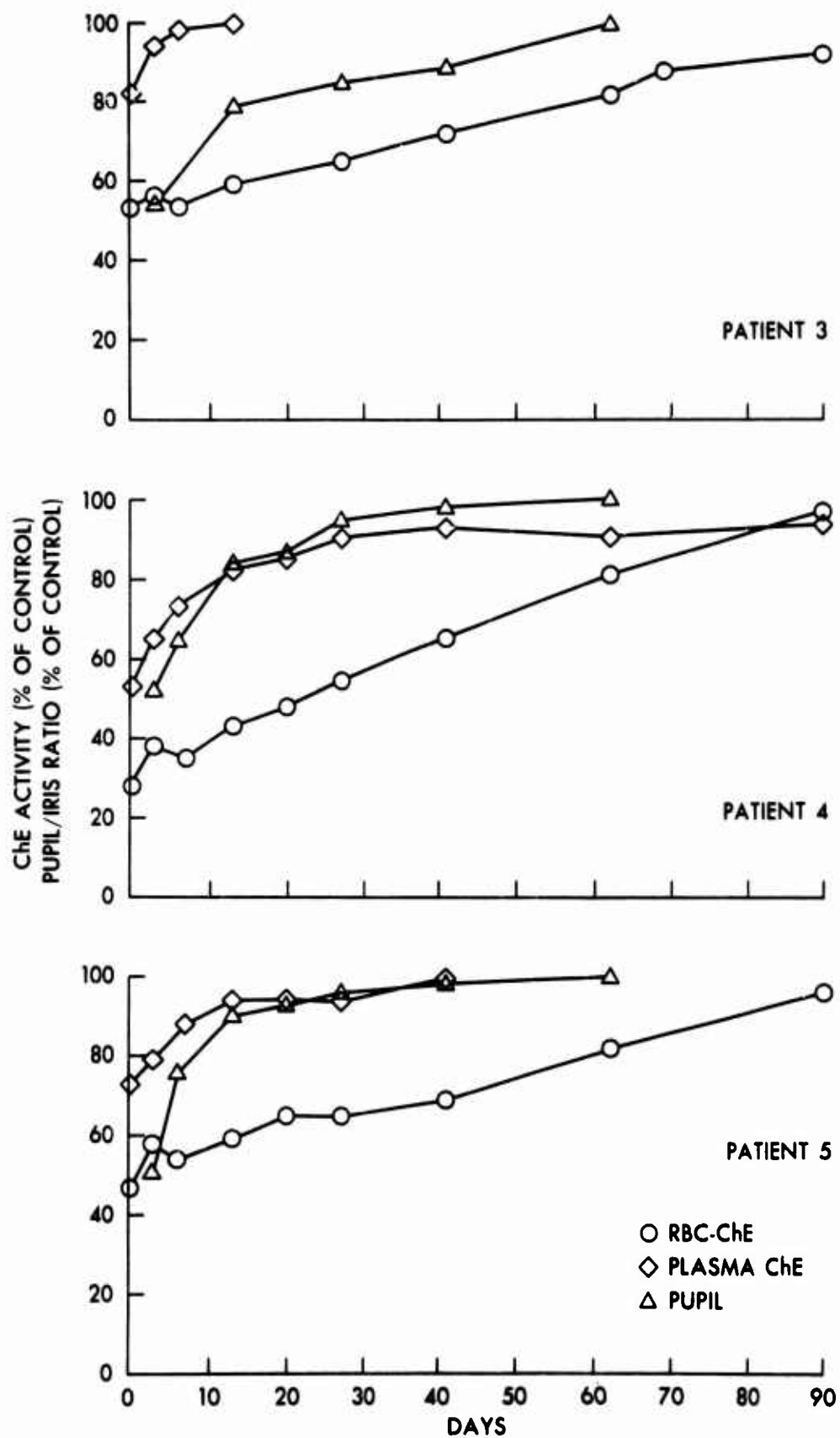


Figure 2: Red Blood Cell and Plasma ChE and Pupil to Iris Ratios (as Described in Text) of Patients 3, 4, and 5.

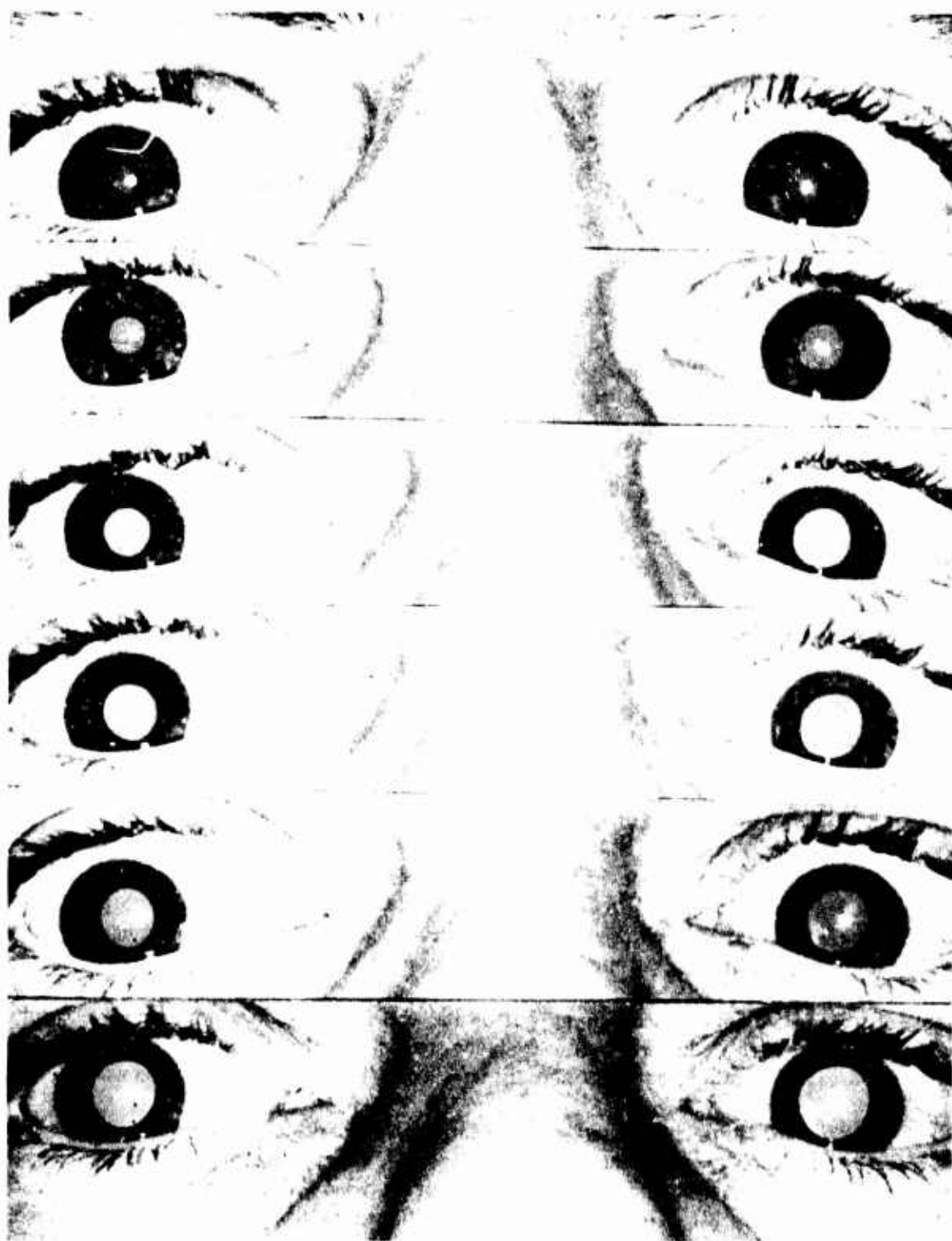


Figure 3: Photographs (Taken after Dark Adaptation, as Described in the Text)
of the Pupils of Subject 3.

The times after exposure, from top to bottom, are 3 days,
6 days, 13 days, 20 days, 41 days, and 62 days.

bronchial gland secretions, an increasing impairment of respiration with apnea and cyanosis, convulsions and death. The miosis, rhinorrhea and bronchoconstriction and increased secretions are probably local effects of the vapor on the involved organs and the former two may occur much later or not at all when the exposure is by another route (e.g., oral). Gastrointestinal signs and symptoms (nausea, vomiting, diarrhea, etc.), may be the predominant manifestations after exposure by some routes (e.g., oral, percutaneous), but may not be seen after vapor exposure unless there is a large systemic absorption.

Bradycardia, expected after antiChE poisoning due to the vagotonic effect of excess acetylcholine, has not been prominent in most reported cases. Presumably factors related to stress and anoxia overcome this expected pharmacological action.

The major immediate goal of therapy in moderate or severe cases of poisoning is to maintain adequate oxygenation. Assisted respiration does this directly and an anticholinergic drug, such as atropine, acts to reduce bronchoconstriction and excess bronchial secretions. The doses of atropine used in the therapy of antiChE intoxication are much larger than those commonly prescribed (e.g., 0.4-0.6 mg), but the dose should be titrated against the effects to maintain a tachycardia and to keep secretions and bronchoconstriction minimal.

A second drug used in the therapy of many antiChE intoxications is an oxime, such as pralidoxime chloride. Certain oximes can displace most antiChE compounds from the enzyme, which can then resume its normal function. The oximes are relatively ineffective against some antiChE compounds because of the rapid irreversible phosphorylation, or aging*, of the inhibitor-enzyme complex.^{5,6}

The side effects of pralidoxime chloride may include hypertension, diplopia, blurred vision, nausea and vomiting. These are dose-related and although they are said¹ to be rare or minimal at therapeutic doses (0.5-2 gm), we have seen them after intravenous doses of 5-10 mg/kg.¹¹ The LD₅₀ of pralidoxime chloride is 190 mg/kg in dogs and is 100 mg/kg in rabbits;¹² the mechanism of death is probably respiratory depression.¹³

The first patient, exposed to what probably was over a lethal dose of soman, had an atypical sudden onset of severe effects about 10 minutes after exposure. With no premonitory symptoms he fell unconscious with signs of systemic intoxication. This early central nervous system manifestation and the trismus and nuchal rigidity may have been because the route of absorption was probably through facial skin and the mucous membranes of the mouth. It has been demonstrated that an antiChE compound put on the skin will cause local muscular hyperactivity and increased sweating at this site before systemic signs or symptoms occur**. His later recurrent bouts of nausea and vomiting were undoubtedly effects of the antiChE compound as well.

His circulating cholinesterases showed little or no response to a usually therapeutic dose of 2-PAMC1, because the soman-enzyme complex becomes refractory to oxime reactivation within minutes.^{5,6} The amount and rate of recovery of his tissue ChE are unknown, but the course of his recovery suggests (a) it recovers more rapidly than the circulating ChE's, or (b) he could function with negligible amounts of tissue ChE.

* This is the process by which the enzyme-inhibitor complex becomes refractory to oxime cleavage and is due to the loss of an alkyl or alkoxy group from the attached inhibitor.

** Sim, V. M., et al. Unpublished data.

This patient had three iatrogenic complications of therapy. The first of these was urinary retention brought about by a dose of atropine probably higher than necessary at the time it was given. Another dose of atropine caused a cardiac arrhythmia (atrial fibrillation) as well as another episode of urinary retention. Catheterization relieved the retention, but introduced infection. To avoid these complications of atropine, another recurrence of vomiting was treated with prochlorperazine. Although the doses given were not excessive, they were adequate to cause extrapyramidal signs and symptoms, typical side effects of phenothiazine therapy. Phenothiazines have been reported to potentiate the effects of an antiChE compound in man⁷ and to decrease the LD₅₀ in animals;⁸ however, these were quite typical of phenothiazine side effects and it is quite possible that the cumulative dose was sufficient to cause them. The undesirable side effects of atropine indicate that although large doses may be used initially, as recovery occurs the drug must be used more judiciously and "titrated" against the clinical response.

The rationale for the use of scopolamine in this patient was the assumption that the mental manifestations were due to excess acetylcholine accumulating because of ChE inhibition and that an anticholinergic compound might block this. Since scopolamine has a relatively higher affinity for the CNS than atropine and has been shown to be effective in reversing CNS changes caused by antiChE's,¹⁴ it was selected for the trial. Methscopolamine was used as a placebo as it produces the peripheral effects of cholinergic blockade, but does not penetrate the CNS presumably because of its quaternary structure.

The patient appeared to benefit from therapy with scopolamine. His mood was better, he was less anxious, he slept more restfully, and he performed better on the NF on the days he received scopolamine. The improvement in performance on drug over that of placebo days is particularly noteworthy as a normal individual will have a noticeable decrement in performance (using the NF) at this dose of scopolamine⁴ and later this patient also had this expected response to scopolamine. His initial paradoxical responses suggest altered cholinergic mechanisms were present in his CNS at the times he initially received this drug and that these altered cholinergic mechanisms were responsible for his mental status.

Whether more prolonged or more intensive treatment with scopolamine would have been of additional benefit and whether scopolamine would have benefited the second patient (who was seen some time before the first) are unknown. Additional trials with scopolamine under these circumstances are indicated.

The second patient had a more typical sequence of events after a vapor exposure: an increase in secretions, bronchoconstriction, miosis, more severe respiratory distress, cyanosis, apnea, muscular fasciculations, and convulsions. He too had prolonged intermittent nausea and vomiting, but he also had repeated episodes of apnea. Whether these latter were related to the large amounts of 2-PAMCl he was given (about 6 gm, or 75-80 mg/kg) can not be determined.

His initial EKG changes (marked depression of the ST segment recorded from all leads) were ischemic changes caused by tachycardia and anoxia. At the time, there was some question of whether the other immediate changes were related to the high dose of pralidoxime chloride, as T wave changes have been seen after oxime administration.¹⁵ However, the subsequent changes were consistent with subendocardial injury or infarction. The findings on autopsy, approximately 18 months later confirmed the fact that the patient had severe sclerosis of the coronary arteries.

The prolonged period of mental depression following his acute episode may have been a direct CNS effect of the antiChE as that of the first patient was. Such sequelae have been reported

previously,^{11, 12} but are not usually emphasized. Although psychiatric and psychological evaluation was not as comprehensive as in the first patient, it might be surmised that other factors were also operative. According to the psychiatrist's reports his mental status was largely concerned with his physical well being, arising no doubt out of his health, and his age.

The last three patients had signs and symptoms typical of a vapor exposure to small amounts of an antiChE: miosis, rhinorrhea, increased salivations, and slight bronchoconstriction. They did not have bradycardia. They are reported to illustrate the recovery of the sarin induced miosis.

The linear recovery of the RBC-ChE with time and the more rapid recovery of plasma ChE correspond to other in vivo data in man.¹⁶ If the phosphorylation of the enzyme is irreversible, this apparent recovery of plasma ChE is thought to represent hepatic synthesis of new enzyme and the apparent RBC-ChE recovery is due to erythropoiesis.¹⁷ It is possible therefore that the functional recovery of the pupillary sphincter is also related to de novo synthesis of ChE at that site.

Conversely, it has been demonstrated that functional recovery of a neuromuscular junction can take place in the absence of measurable enzyme activity at that site,^{18, 19} and this may have taken place in these subjects. Unless tissue ChE synthesis is rapid, this would seem the more likely explanation, at least in the second patient who had a prompt return of physical function while his circulating cholinesterase activity was negligible because of an apparently overwhelming dose of soman.

IV. CONCLUSIONS.

Four patients were accidentally exposed to the cholinesterase inhibitor sarin and one was similarly exposed to soman.

The two with the most severe intoxication (one to each compound) had psychiatric sequelae persisting for many weeks. Scopolamine, which disrupts mental performance in normal subjects, ameliorated the mental condition in the one patient to whom it was administered. The therapeutic effectiveness of this cholinergic blocking compound with a relatively high CNS affinity suggests that these sequelae were the direct result of excess cholinergic stimulation. This drug deserves further evaluation under similar circumstances.

The soman-inhibited circulating cholinesterases of one patient were refractory to reactivation by the oxime 2-pyridinium aldoxime methochloride in a dose that is usually effective. Despite this, the patient's clinical recovery was consistent with the severity of his intoxication. This suggests that the activity of the circulating cholinesterases does not parallel the activity of cholinesterase in tissue, or that tissue function can be reasonably normal with a minimal amount of cholinesterase activity.

The recovery of the ability of the pupils' ability to dilate was followed in three patients who had mild intoxication with sarin. The time course of recovery was much the same as plasma cholinesterase recovery: initially rapid with about two-thirds of the activity restored in two weeks. However recovery was not complete for several months.

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